PATENT COOPERATION TREA

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| X-11704 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US 00/ 02502 | 09/02/2000 | 10/02/1999 |
| Applicant | | |
| ELI LILLY AND COMPANY et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. =

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/02502

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/22 C07D405/12 A61K31/445 C07D401/06 C07D409/12
C07D401/12 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP 0 832 650 A (LILLY CO ELI)<br>1 April 1998 (1998-04-01)<br>claim 3 | 1,10-12 |
| A | EP 0 733 628 A (LILLY CO ELI)<br>25 September 1996 (1996-09-25)<br>abstract | 1,10-12 |
| A | WO 95 00131 A (CAMBRIDGE NEUROSCIENCE INC<br>;UNIV VIRGINIA COMMONWEALTH (US); GLENN)<br>5 January 1995 (1995-01-05)<br>page 54; claim 1 | 1,10 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 July 2000 | 03/08/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | De Jong, B |

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | ADHAM N ET AL: "CLONING OF ANOTHER HUMAN SEROTONIN RECEPTOR (5-HT1F): A FIFTH 5-HT1RECEPTOR SUBTYPE COUPLED TO THE INHIBITION OF ADENYLATE CYCLASE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 90, no. 2, 15 January 1993 (1993-01-15), pages 408-412, XP000572279 ISSN: 0027-8424 table 1 | |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/02502

**Box I Observations where c rtain claims were found unsearchable (Continuation f Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

REC'D 11 APR 2001
WIPO PCT

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| X-11704 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/02502 | 09/02/2000 | 10/02/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C07D211/00 | | |
| Applicant<br>ELI LILLY AND COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| [23/08/2000] 01.09.2000 | 05.04.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Traegler-Goeldel, M<br>Telephone No. +49 89 2399 8278 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/02502

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-16 as originally filed

**Claims, No.:**

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-13.

because:

☒ the said international application, or the said claims Nos. 11-13 relate to the following subject matter which does not require an international preliminary examination (*specify*):
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-17 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 14-17 |

No: Claims

2. Citations and explanations
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

re Item III:

Claims 11 to 13 have to be considered as being directed to a method for the treatment of the human or animal body. Under the terms of Rule 67.1 (iv) and Article 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examinations on such claims concerning industrial applicability.

re Item V:

1. Prior art

The Preliminary Examination procedure is based on the documents cited in the International Search Report:

| | |
|---|---|
| EP-A 0832 650 | D1 |
| EP-A 0733 628 | D2 |
| WO-A 95 00131 | D3 |
| Proc. Natl. Acad. Sci. USA 1993; 90; pp. 408-412 | D4. |

2. Novelty

The claimed compounds are substituted 4-benzoylpiperidine derivatives, whereas those disclosed in documents D1 and D2 are 3-(piperidin-4-yl)- and 3-(1,2,3,6-tetrahydropyridin-4-yl)-1h-indole derivatives and those disclosed in D3 are 1-4-substituted piperidine derivatives, the structural closest of which (first compound on p. 54) differs form the claim ones by the absence of a residue corresponding to $R^1$ in the present application. Document D4 describes isolation and characterisation of the new 5-$HT_1$ receptor subtype 5-$HT_{1F}$. Thus the claimed subject matter of claims 1 to 17 are considered to fulfil the requirements of Art. 33 (2) PCT with respect to the cited prior art.

3. Inventive step

Whereas document D3 is concerned with piperidine-4-derivatives which are sigma receptor ligands useful for neurological disorders and D4 is concerned with cloning of the new 5-$HT_{1F}$ receptor, documents D1 and D2 are concerned with compounds useful

in the treatment of migraine due to their agonistic activity on said 5-$HT_{1F}$ receptor, as are those of the present application. Thus the closest prior art is to be seen in documents D1 and D2. The compounds of the present application differ structurally considerably from those according to D1 and D2: whereas the compounds according to D1 and D2 are 3-(piperidin-4-yl)- and 3-(1,2,3,6-tetra-hydropyridin-4-yl)-1h-indole derivatives, the present ones are substituted 4-benzoylpiperidine derivatives.

Therefore, the problem underlying the present application is to be seen in the provision of further compounds useful in the treatment of migraine due to its activity as potent agonists of the 5-$HT_{1F}$ receptor. The solution of this problem as set out in the present application is to be seen in the provision of compounds of formula I as specified in the description and exemplified by the examples. As far as specified compounds are concerned, this solution could be considered to involve an inventive step, since documents D1 and D2, concerned with compounds that show the same activity but are structurally very different, would not have led the skilled person to replace the indole moiety by a 3-substituted benzoyl moiety as in the present application to result with the claimed substituted 4-benzoylpiperidine derivatives with the alleged activity.

Nevertheless, it is not credible that this problem has been solved by the whole scope of the claimed subject matter (i.e. comprised by the whole breadth of claim 1) and in as far as all compounds are concerned comprised by the unspecified expressions "heteroaryl" and especially "optionally substituted" in the definition of residues Ar, $Ar^1$, $Ar^2$, $Ar^3$, $Ar^4$, $R^3$, $R^4$, $R^5$, and $R^6$, since the claimed area, i.e. the vast number of theoretically conceivable compounds comprised under formula I of claim 1, can clearly not be considered to represent any reasonable generalization or obvious modifications or equivalents of the examples (e.g. heteroaryl only exemplified as pyridyl, furyl and thienyl) given in the description. Furthermore the objected expressions also concern residues or substituents of residues, which represent essential features. In this context it is brought to the Applicant's attention that according to the PCT Preliminary Examination Guidelines, Section IV, C III, 6., especially 6.1, 6.2 and 6.4 the breadth of the claims should be such, that all the comprised compounds could be expected to solve the problem according to Art. 33 (3) PCT, i.e. that the alleged effect must be convincingly shown to be indeed present for the whole claimed range and the objected expressions, as far as they remain in any new claim, should be specified according to the specification as originally filed. Therefore, the only problem which has obviously

been solved by this part of the the present application can only be seen in the provision of new compounds. Since the solution of this problem is obvious for the skilled person, claims 1 to 17 cannot be considered to fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No objection arises as far as the claimed compounds may be used for the production of pharmaceuticals.

re Item VIII:

1. Claims

a, The expressions "heteroaryl" and "optionally substituted" in the definitions in claim 1 without further specification of these terms are unlimited and not considered to represent obvious modifications or equivalents of the examples given in the description (according to the PCT Preliminary Examination Guidelines, C III, 6., especially 6.1, 6.2 and 6.4). Furthermore, according to the PCT Preliminary Examination Guidelines, CIII, 4.1 and 4.2, the meaning of a claim should be clear from the wording of the claim alone. If special meanings do apply, the meaning should be clear from the claims alone. This is definitely not the case for e.g. the expression "heteroaryl" or "optionally substituted". Thus, the subject matter of the claims concerned does not fulfil the requirements according to Art. 6 PCT.

b, Claims 10 to 12 do not fulfil the requirements of Art. 6, Rule 3 and Rule 13 PCT according to the PCT International Preliminary Examination Guidelines, CIII-1, 2 and 3 since they do not contain a reference to main claim 1.

PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| X-11704 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/02502 | 09/02/2000 | 10/02/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C07D211/00 | | |
| Applicant<br>ELI LILLY AND COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

CORRECTED VERSION

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 23/08/2000 | 18.05.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Traegler-Goeldel, M<br>Telephone No. +49 89 2399 8278 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/02502

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-16 as originally filed

**Claims, No.:**

1-17 with telefax of 16/04/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*
**see separate sheet**

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-13.

because:

☒ the said international application, or the said claims Nos. 11-13 relate to the following subject matter which does not require an international preliminary examination (*specify*):
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-17 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 14-17 |

No: Claims

2. Citations and explanations
   **see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**s e separate sheet**

re Item I:

The following amendments in claims 1 and 14 do not fulfil the requirements of Rule 70.2 (c) PCT, since they go beyond the disclosure as originally filed:

In the description as originally filed the term substituted heterocycle and substituted heteroaryl is meant to be substituted with up to three substituents (see p. 6, l. 15 to 18 and l. 30). This can neither be considered as being a specifically disclosed basis for the definition of heterocycle being substituted by 1, 2 or 3 substituents nor for the definition of heteroaryl being substituted by 0, 1, 2, or 3 substituents (by the way this definition is different from that for heterocycle but the basis in the description being the same), since the specific values of 0, 1 and 2 have never been mentioned explicitly.

The same applies in principle for the definition of substituted alkyl as being substituted 1, 2 or 3 times by specific substituents, the basis being that it may be substituted 1 to 3 times; the value of 2 has not been explicitly mentioned in the description.

Therefore, the present application will be considered as if these amendments have not been made.

re Item III:

Claims 11 to 13 have to be considered as being directed to a method for the treatment of the human or animal body. Under the terms of Rule 67.1 (iv) and Article 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examinations on such claims concerning industrial applicability.

re Item V:

1. Prior art

The Preliminary Examination procedure is based on the documents cited in the International Search Report:

EP-A 0832 650 D1

| | |
|---|---|
| EP-A 0733 628 | D2 |
| WO-A 95 00131 | D3 |
| Proc. Natl. Acad. Sci. USA 1993; 90; pp. 408-412 | D4. |

2. Novelty

The claimed compounds are substituted 4-benzoylpiperidine derivatives, whereas those disclosed in documents D1 and D2 are 3-(piperidin-4-yl)- and 3-(1,2,3,6-tetra-hydropyridin-4-yl)-1h-indole derivatives and those disclosed in D3 are 1-4-substituted piperidine derivatives, the structural closest of which (first compound on p. 54) differs form the claim ones by the absence of a residue corresponding to $R^1$ in the present application. Document D4 describes isolation and characterisation of the new 5-$HT_1$ receptor subtype 5-$HT_{1F}$. Thus the claimed subject matter of claims 1 to 17 are considered to fulfil the requirements of Art. 33 (2) PCT with respect to the cited prior art.

3. Inventive step

Whereas document D3 is concerned with piperidine-4-derivatives which are sigma receptor ligands useful for neurological disorders and D4 is concerned with cloning of the new 5-$HT_{1F}$ receptor, documents D1 and D2 are concerned with compounds useful in the treatment of migraine due to their agonistic activity on said 5-$HT_{1F}$ receptor, as are those of the present application. Thus the closest prior art is to be seen in documents D1 and D2. The compounds of the present application differ structurally considerably from those according to D1 and D2: whereas the compounds according to D1 and D2 are 3-(piperidin-4-yl)- and 3-(1,2,3,6-tetra-hydropyridin-4-yl)-1h-indole derivatives, the present ones are substituted 4-benzoylpiperidine derivatives.

Therefore, the problem underlying the present application is to be seen in the provision of further compounds useful in the treatment of migraine due to its activity as potent agonists of the 5-$HT_{1F}$ receptor. The solution of this problem as set out in the present application is to be seen in the provision of compounds of formula I as specified in the description and exemplified by the examples. As far as specified compounds are concerned, this solution could be considered to involve an inventive step, since documents D1 and D2, concerned with compounds that show the same activity but are structurally very different, would not have led the skilled person to replace the indole

moiety by a 3-substituted benzoyl moiety as in the present application to result with the claimed substituted 4-benzoylpiperidine derivatives with the alleged activity.

Nevertheless, it is not credible that this problem has been solved by the whole scope of the claimed subject matter (i.e. comprised by the whole breadth of claim 1) and in as far as all compounds are concerned comprised by the unspecified expressions "heteroaryl" (in claims 11 and 12) and "optionally substituted" in the definition of residues Ar, $Ar^1$, $Ar^2$, $Ar^3$, $Ar^4$, $R^3$, $R^4$, $R^5$, and $R^6$ in claims 1, 11, 12 and 14 since the claimed area, i.e. the vast number of theoretically conceivable compounds comprised under formula I of claim 1, can clearly not be considered to represent any reasonable generalization or obvious modifications or equivalents of the examples given in the description. Furthermore the objected expressions also concern residues or substituents of residues, which represent essential features. In this context it is brought to the Applicant's attention that according to the PCT Preliminary Examination Guidelines, Section IV, C III, 6., especially 6.1, 6.2 and 6.4 the breadth of the claims should be such, that all the comprised compounds could be expected to solve the problem according to Art. 33 (3) PCT. The objected expressions, as far as they remain in any new claim, should have been specified according to the specification as originally filed: in the present case "heteroaryl" and "optionaly substituted phenyl" in claims 11 and 12 should have been defined as in present claim 1, "optionally substituted" with the term "is substituted with up to three substituents independently selected from..." for the specified heterocyclic and heteroaryl residues, and "may be substituted 1 to 3 times" for the alkyl residues in claims 1, 11, 12 and 14. But the objected terms "optionally substituted" and "heteroaryl" (claims 11 and 12) have not been specified according to the description as originally filed.

Therefore, the only problem which has obviously been solved by this part of the the present application can only be seen in the provision of new compounds. Since the solution of this problem is obvious for the skilled person, claims 1 to 17 cannot be considered to fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No objection arises as far as the claimed compounds may be used for the production of pharmaceuticals.

re Item VIII:

1. Claims

a, The expression "optionally substituted" in the definitions in claims 1, 11, 12 and 14 and "heteroaryl" in claim 12 without further specification of these terms are unlimited and not considered to represent obvious modifications or equivalents of the examples given in the description (according to the PCT Preliminary Examination Guidelines, C III, 6., especially 6.1, 6.2 and 6.4). Furthermore, according to the PCT Preliminary Examination Guidelines, CIII, 4.1 and 4.2, the meaning of a claim should be clear from the wording of the claim alone. If special meanings do apply, the meaning should be clear from the claims alone. This is definitely not the case for e.g. the expression "heteroaryl" (still present in claims 11 and 12) or "optionally substituted". Thus, the subject matter of the claims concerned does not fulfil the requirements according to Art. 6 PCT.

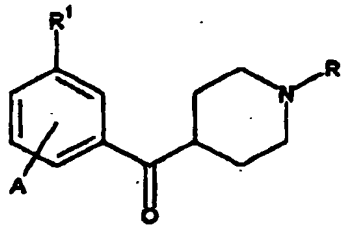
b, Claims 11 to 12 do not fulfil the requirements of Art. 6, Rule 3 and Rule 13 PCT according to the PCT International Preliminary Examination Guidelines, CIII-1, 2 and 3 since they do not contain a reference to main claim 1.

X-11704



WE CLAIM:

1. A compound of formula I:



I;

or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl, or ($C_1$-$C_6$ alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

$R^2$ is -CO-, -CS-, or $-SO_2-$;

$R^3$ is hydrogen, $C_1$-$C_6$ alkyl, optionally substituted with $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$;

or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring;

wherein substituted phenyl is phenyl mono-substituted with a substituent selected from the group consisting of halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, phenyl, benzoyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, ($C_1$-$C_4$ alkyl)$S(O)_n$, ($C_1$-$C_4$ alkyl)$_2$ amino, $C_1$-$C_4$ acyl, or two or three substituents independently selected from the group consisting of halo, nitro, trifluoromethyl, $C_1$-$C_4$ alkyl, and $C_1$-$C_4$ alkoxy;

n is 0, 1, or 2;

heteroaryl is an aromatic or benzofused aromatic 5 or 6 membered ring containing 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur;

substituted heteroaryl is heteroaryl substituted with 1, 2, or 3 substituents selected from the group consisting of halo, cyano, nitro, hydroxy, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, ($C_1$-$C_4$ alkyl)-S(O)$_n$-, and phenyl-S(O)$_n$-;

substituted alkyl is alkyl substituted 1, 2, or 3 times independently with a substituent selected from the group consisting of halo, hydroxy, phenyl, 2-phenylethylen-1-yl, diphenylmethyl, naphthyl, substituted phenyl, aryloxy, heterocycle, heteroaryloxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, phenyl($C_1$-$C_4$ alkyl), substituted phenyl($C_1$-$C_4$ alkyl), and benzofused $C_4$-$C_8$ cycloalkyl;

heterocycle is aromatic or non-aromatic 5 or 6 membered ring containing 1, 2 or 3 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, said ring being optionally benzofused and said ring or benzofused ring being substituted with 0, 1, 2, or 3 substituents selected from the groups consisting of halo, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, cyano, nitro, hydroxy, ($C_1$-$C_4$ alkyl)-S(O)$_n$-, and phenyl-S(O)$_n$-.

2. The compound of Claim 1 wherein A is hydrogen.

3. The compound of either of Claims 1 or 2 wherein R is methyl.

4. The compound of any of Claims 1-3 wherein $R_1$ is -NH-$R^2$-$R^3$.

5. The compound of any of Claims 1-4 wherein $R^2$ is C=O.

6. The compound of any of Claims 1-5 wherein $R^3$ is $Ar^3$.

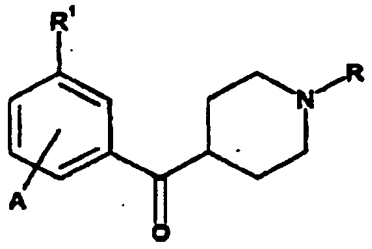
7. The compound of any of Claims 1-6 wherein $Ar^3$ is 4-fluorophenyl.

8. The compound of any of Claims 1-6 wherein $Ar^3$ is 4-fluorophenyl additionally mono- or disubstituted.

9. The compound of any of Claims 1-6 wherein $Ar^3$ is selected from the group consisting of 2-iodo-4-fluorophenyl, 2-bromo-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2,4-difluorophenyl, and 2-methyl-4-fluorophenyl.

10. A pharmaceutical formulation comprising a compound of formula I of claim 1, or a pharmaceutical acid addition salt thereof, and a pharmaceutical carrier, diluent, or excipient.

11. A method for activating 5-$HT_{1F}$ receptors in mammals comprising administering to a mammal in need of such activation an effective amount of a compound of formula I:



I;

or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1$-$C_6$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl, or ($C_1$-$C_6$ alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

$R^2$ is -CO-, -CS-, or $-SO_2-$;

$R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring.

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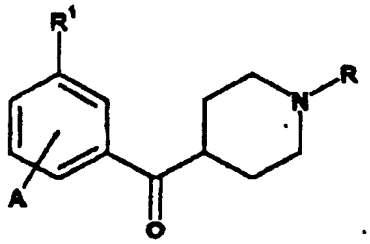
12. A method for inhibiting neuronal protein extravasation comprising administering to a mammal in need of such inhibition an effective amount of a compound of formula I:



I;

or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl, or ($C_1$-$C_6$ alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

$R^2$ is -CO-, -CS-, or $-SO_2-$;

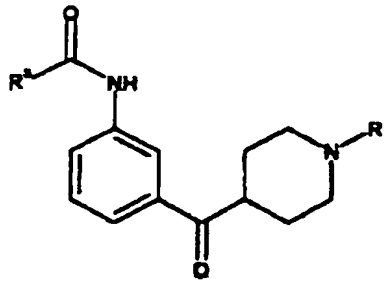
$R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring.

13. The method according to either of Claims 11 or Claim 12 where the mammal is a human.

14. A process of making the compounds of formula I(a):



I(a)

wherein $R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$;

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring; and

$Ar^3$ and $Ar^4$ are independently an optionally substituted phenyl or optionally substituted heteroaryl;

wherein substituted phenyl is phenyl mono-substituted with a substituent selected from the group consisting of halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, phenyl, benzoyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, ($C_1$-$C_4$ alkyl)$S(O)_n$, ($C_1$-$C_4$ alkyl)$_2$ amino, $C_1$-$C_4$ acyl, or two or three substituents independently selected from the group consisting of halo, nitro, trifluoromethyl, $C_1$-$C_4$ alkyl, and $C_1$-$C_4$ alkoxy;

n is 0, 1, or 2;

heteroaryl is an aromatic or benzofused aromatic 5 or 6 membered ring containing 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur;

substituted heteroaryl is heteroaryl substituted with 1, 2, or 3 substituents selected from the group consisting of halo, cyano, nitro, hydroxy, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, ($C_1$-$C_4$ alkyl)-$S(O)_n$-, and phenyl-$S(O)_n$-;

substituted alkyl is alkyl substituted 1, 2, or 3 times independently with a substituent selected from the group consisting of halo, hydroxy, phenyl, 2-phenylethylen-1-yl, diphenylmethyl, naphthyl, substituted phenyl, aryloxy, heterocycle, heteroaryloxy, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, phenyl($C_1$-$C_4$ alkyl), substituted phenyl($C_1$-$C_4$ alkyl), and benzofused $C_4$-$C_8$ cycloalkyl;

heterocycle is aromatic or non-aromatic 5 or 6 membered ring containing 1, 2 or 3 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, said ring being optionally benzofused and said ring or benzofused ring being substituted with 0, 1, 2, or 3 substituents selected from the groups consisting of halo, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, cyano, nitro, hydroxy, ($C_1$-$C_4$ alkyl)-S(O)$_n$-, and phenyl-S(O)$_n$-;

comprising:

(a) protecting 4-benzoylpiperidine hydrochloride to form an N-protected 4-benzoylpiperidine hydrochloride;

(b) nitrating the N-protected 4-benzoylpiperidine hydrochloride to form a mixture of N-protected 4-(mono nitrobenzoyl)piperidines;

(c) deprotecting the N-protected 4-(mononitrobenzoyl)-piperidine mixture to form a mixture of 4-(mononitrobenzoyl)piperidines;

(d) separating the 4-(3-nitrobenzoyl)piperidine from the mixture of 4-(mononitrobenzoyl)piperidines;

(e) reducing the 4-(3-nitrobenzoyl)piperidine to form 4-(3-aminobenzoyl)piperidine; and

(f) acylating the 4-(3-aminobenzoyl)piperidine.

15. The process of Claim 14 wherein steps a) and b) are combined.

16. The process of any of Claims 14-15 wherein the source of the protecting group of step a) is trifluoroacetic anhydride.

17. The process of any of Claims 14-16 wherein the source of the nitronium ion is ammonium nitrate.

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED
MAY 29 2001
ELI LILLY & COMPANY
PATENT DIVISION

# PCT

To:

TITUS, Robert D
ELI LILLY AND COMPANY
Lilly Corporate Center
++++++++++++++++++++++++++++++++++
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 18.05.2001 |
| Applicant's or agent's file reference<br>X-11704 | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US00/02502 | 09/02/2000 | 10/02/1999 |

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Ambroa, J.R.<br><br>Tel.+49 89 2399-8012 |

Form PCT/IPEA/416 (July 1992)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| X-11704 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/02502 | 09/02/2000 | 10/02/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C07D211/00 | | |
| Applicant<br>ELI LILLY AND COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 23/08/2000 | 18.05.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Traegler-Goeldel, M<br>Telephone No. +49 89 2399 8278 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/02502

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

| | | |
|---|---|---|
| 1-16 | as originally filed | |

**Claims, No.:**

| | | |
|---|---|---|
| 1-17 | with telefax of | 16/04/2001 |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*
**see separate sheet**

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-13.

because:

☒ the said international application, or the said claims Nos. 11-13 relate to the following subject matter which does not require an international preliminary examination (*specify*):
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-17 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 14-17 |

No: Claims

2. Citations and explanations
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

re Item I:

The following amendments in claims 1 and 14 do not fulfil the requirements of Rule 70.2 (c) PCT, since they go beyond the disclosure as originally filed:

In the description as originally filed the term substituted heterocycle and substituted heteroaryl is meant to be substituted with up to three substituents (see p. 6, l. 15 to 18 and l. 30). This can neither be considered as being a specifically disclosed basis for the definition of heterocycle being substituted by 1, 2 or 3 substituents nor for the definition of heteroaryl being substituted by 0, 1, 2, or 3 substituents (by the way this definition is different from that for heterocycle but the basis in the description being the same), since the specific values of 0, 1 and 2 have never been mentioned explicitly.

The same applies in principle for the definition of substituted alkyl as being substituted 1, 2 or 3 times by specific substituents, the basis being that it may be substituted 1 to 3 times; the value of 2 has not been explicitly mentioned in the description.

Therefore, the present application will be considered as if these amendments have not been made.

re Item III:

Claims 11 to 13 have to be considered as being directed to a method for the treatment of the human or animal body. Under the terms of Rule 67.1 (iv) and Article 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examinations on such claims concerning industrial applicability.

re Item V:

1. Prior art

The Preliminary Examination procedure is based on the documents cited in the International Search Report:

EP-A 0832 650 D1

| | |
|---|---|
| EP-A 0733 628 | D2 |
| WO-A 95 00131 | D3 |
| Proc. Natl. Acad. Sci. USA 1993; 90; pp. 408-412 | D4. |

2. Novelty

The claimed compounds are substituted 4-benzoylpiperidine derivatives, whereas those disclosed in documents D1 and D2 are 3-(piperidin-4-yl)- and 3-(1,2,3,6-tetra-hydropyridin-4-yl)-1h-indole derivatives and those disclosed in D3 are 1-4-substituted piperidine derivatives, the structural closest of which (first compound on p. 54) differs form the claim ones by the absence of a residue corresponding to $R^1$ in the present application. Document D4 describes isolation and characterisation of the new 5-$HT_1$ receptor subtype 5-$HT_{1F}$. Thus the claimed subject matter of claims 1 to 17 are considered to fulfil the requirements of Art. 33 (2) PCT with respect to the cited prior art.

3. Inventive step

Whereas document D3 is concerned with piperidine-4-derivatives which are sigma receptor ligands useful for neurological disorders and D4 is concerned with cloning of the new 5-$HT_{1F}$ receptor, documents D1 and D2 are concerned with compounds useful in the treatment of migraine due to their agonistic activity on said 5-$HT_{1F}$ receptor, as are those of the present application. Thus the closest prior art is to be seen in documents D1 and D2. The compounds of the present application differ structurally considerably from those according to D1 and D2: whereas the compounds according to D1 and D2 are 3-(piperidin-4-yl)- and 3-(1,2,3,6-tetra-hydropyridin-4-yl)-1h-indole derivatives, the present ones are substituted 4-benzoylpiperidine derivatives.

Therefore, the problem underlying the present application is to be seen in the provision of further compounds useful in the treatment of migraine due to its activity as potent agonists of the 5-$HT_{1F}$ receptor. The solution of this problem as set out in the present application is to be seen in the provision of compounds of formula I as specified in the description and exemplified by the examples. As far as specified compounds are concerned, this solution could be considered to involve an inventive step, since documents D1 and D2, concerned with compounds that show the same activity but are structurally very different, would not have led the skilled person to replace the indole

moiety by a 3-substituted benzoyl moiety as in the present application to result with the claimed substituted 4-benzoylpiperidine derivatives with the alleged activity.

Nevertheless, it is not credible that this problem has been solved by the whole scope of the claimed subject matter (i.e. comprised by the whole breadth of claim 1) and in as far as all compounds are concerned comprised by the unspecified expressions "heteroaryl" (in claims 11 and 12) and "optionally substituted" in the definition of residues Ar, $Ar^1$, $Ar^2$, $Ar^3$, $Ar^4$, $R^3$, $R^4$, $R^5$, and $R^6$ in claims 1, 11, 12 and 14 since the claimed area, i.e. the vast number of theoretically conceivable compounds comprised under formula I of claim 1, can clearly not be considered to represent any reasonable generalization or obvious modifications or equivalents of the examples given in the description. Furthermore the objected expressions also concern residues or substituents of residues, which represent essential features. In this context it is brought to the Applicant's attention that according to the PCT Preliminary Examination Guidelines, Section IV, C III, 6., especially 6.1, 6.2 and 6.4 the breadth of the claims should be such, that all the comprised compounds could be expected to solve the problem according to Art. 33 (3) PCT. The objected expressions, as far as they remain in any new claim, should have been specified according to the specification as originally filed: in the present case "heteroaryl" and "optionaly substituted phenyl" in claims 11 and 12 should have been defined as in present claim 1, "optionally substituted" with the term "is substituted with up to three substituents independently selected from..." for the specified heterocyclic and heteroaryl residues, and "may be substituted 1 to 3 times" for the alkyl residues in claims 1, 11, 12 and 14. But the objected terms "optionally substituted" and "heteroaryl" (claims 11 and 12) have not been specified according to the description as originally filed.

Therefore, the only problem which has obviously been solved by this part of the the present application can only be seen in the provision of new compounds. Since the solution of this problem is obvious for the skilled person, claims 1 to 17 cannot be considered to fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No objection arises as far as the claimed compounds may be used for the production of pharmaceuticals.

re Item VIII:

1. Claims

a, The expression "optionally substituted" in the definitions in claims 1, 11, 12 and 14 and "heteroaryl" in claim 12 without further specification of these terms are unlimited and not considered to represent obvious modifications or equivalents of the examples given in the description (according to the PCT Preliminary Examination Guidelines, C III, 6., especially 6.1, 6.2 and 6.4). Furthermore, according to the PCT Preliminary Examination Guidelines, CIII, 4.1 and 4.2, the meaning of a claim should be clear from the wording of the claim alone. If special meanings do apply, the meaning should be clear from the claims alone. This is definitely not the case for e.g. the expression "heteroaryl" (still present in claims 11 and 12) or "optionally substituted". Thus, the subject matter of the claims concerned does not fulfil the requirements according to Art. 6 PCT.

b, Claims 11 to 12 do not fulfil the requirements of Art. 6, Rule 3 and Rule 13 PCT according to the PCT International Preliminary Examination Guidelines, CIII-1, 2 and 3 since they do not contain a reference to main claim 1.

PATENT COOPERATION TREAT

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| X-11704 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US 00/ 02502 | 09/02/2000 | 10/02/1999 |
| Applicant | | |
| ELI LILLY AND COMPANY et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/02502

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/22 C07D405/12 A61K31/445 C07D401/06 C07D409/12
C07D401/12 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP 0 832 650 A (LILLY CO ELI)<br>1 April 1998 (1998-04-01)<br>claim 3<br>--- | 1,10-12 |
| A | EP 0 733 628 A (LILLY CO ELI)<br>25 September 1996 (1996-09-25)<br>abstract<br>--- | 1,10-12 |
| A | WO 95 00131 A (CAMBRIDGE NEUROSCIENCE INC<br>;UNIV VIRGINIA COMMONWEALTH (US); GLENN)<br>5 January 1995 (1995-01-05)<br>page 54; claim 1<br>---<br>-/-- | 1,10 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 July 2000 | 03/08/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | De Jong, B |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | ADHAM N ET AL: "CLONING OF ANOTHER HUMAN SEROTONIN RECEPTOR (5-HT1F): A FIFTH 5-HT1RECEPTOR SUBTYPE COUPLED TO THE INHIBITION OF ADENYLATE CYCLASE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 90, no. 2, 15 January 1993 (1993-01-15), pages 408-412, XP000572279 ISSN: 0027-8424 table 1 | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/02502

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0832650 A | 01-04-1998 | AU 4074897 A | 14-04-1998 |
| | | WO 9811895 A | 26-03-1998 |
| EP 0733628 A | 25-09-1996 | AU 702322 B | 18-02-1999 |
| | | AU 5311296 A | 08-10-1996 |
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| | | CA 2215322 A | 26-09-1996 |
| | | CN 1184425 A | 10-06-1998 |
| | | CZ 9702888 A | 18-02-1998 |
| | | HU 9800417 A | 28-06-1999 |
| | | JP 11502816 T | 09-03-1999 |
| | | NO 974220 A | 04-11-1997 |
| | | NZ 305166 A | 23-12-1998 |
| | | PL 322843 A | 16-02-1998 |
| | | WO 9629075 A | 26-09-1996 |
| | | US 5708008 A | 13-01-1998 |
| | | US 5962474 A | 05-10-1999 |
| WO 9500131 A | 05-01-1995 | AU 7177694 A | 17-01-1995 |
| | | CA 2166100 A | 05-01-1995 |
| | | EP 0714292 A | 05-06-1996 |
| | | ZA 9404513 A | 16-01-1996 |

(12) INTERNATIONAL APPL ON PUBLISHED UNDER THE PATENT C RATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) Internati nal Publication Date
17 August 2000 (17.08.2000)

PCT

(10) International Publication Number
WO 00/47559 A3

(51) International Patent Classification[7]: C07D 211/22, 405/12, A61K 31/445, C07D 401/06, 409/12, 401/12, A61P 25/06

(21) International Application Number: PCT/US00/02502

(22) International Filing Date: 9 February 2000 (09.02.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/119,596 10 February 1999 (10.02.1999) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KRUSHINSKI, Joseph, Herman, Jr.** [US/US]; 1633 Beckenbauer Way, Indianapolis, IN 46214 (US). **MANCUSO, Vincent** [BE/BE]; 27, Rue des Hauts-Pres, B-5651 Thy-le-Chateau (BE). **NAPORA, Freddy, Andre** [BE/BE]; 9, Rue du Bois, B-5030 Gembloux (BE). **SCHAUS, John, Mehnert** [US/US]; 135 Raintree Drive, Zionsville, IN 46077 (US).

(74) Agents: **TITUS, Robert, D.** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

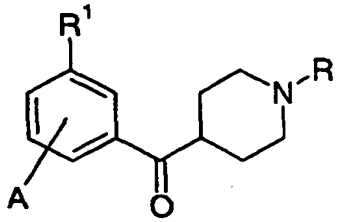
**Published:**
— *With international search report.*

(88) Date of publication of the international search report:
30 November 2000

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: 5-HT$_1$F AGONISTS

WO 00/47559 A3




(I)

(57) Abstract: The present invention relates to a compound of formula (I) and a process for making; or a pharmaceutical acid addition salt thereof; which are useful for activating 5-HT$_{1F}$ receptors and inhibiting neuronal protein extravasation in a mammal.

# INTERNATIONAL SEARCH REPORT

Inte[redacted]pplication No
PCT/[redacted]00/02502

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 C07D211/22 C07D405/12 A61K31/445 C07D401/06 C07D409/12
C07D401/12 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 26 July 2000 | 03/08/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | De Jong, B |

Form PCT ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inte[redacted]lo[redacted]pplication No
PCT/[redacted]0/02502

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Information [redacted]tent family members

Int. [redacted] Application No
PCT/[redacted]00/02502

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| EP 0832650 A | 01-04-1998 | AU 4074897 A | 14-04-1998 |
| | | WO 9811895 A | 26-03-1998 |
| EP 0733628 A | 25-09-1996 | AU 702322 B | 18-02-1999 |
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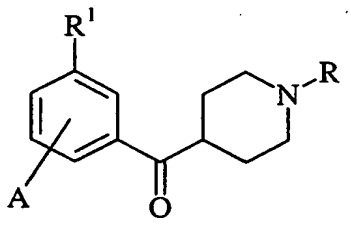
| | | BR 9601061 A | 06-01-1998 |
| | | CA 2215322 A | 26-09-1996 |
| | | CN 1184425 A | 10-06-1998 |
| | | CZ 9702888 A | 18-02-1998 |
| | | HU 9800417 A | 28-06-1999 |
| | | JP 11502816 T | 09-03-1999 |
| | | NO 974220 A | 04-11-1997 |
| | | NZ 305166 A | 23-12-1998 |
| | | PL 322843 A | 16-02-1998 |
| | | WO 9629075 A | 26-09-1996 |
| | | US 5708008 A | 13-01-1998 |
| | | US 5962474 A | 05-10-1999 |
| WO 9500131 A | 05-01-1995 | AU 7177694 A | 17-01-1995 |
| | | CA 2166100 A | 05-01-1995 |
| | | EP 0714292 A | 05-06-1996 |
| | | ZA 9404513 A | 16-01-1996 |

WE CLAIM:

1. A compound of formula I:



I;

or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl, or (C1-C6 alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

$R^2$ is -CO-, -CS-, or $-SO_2-$;

$R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring.

2. The compound of Claim 1 wherein A is hydrogen.

3. The compound of either of Claims 1 or 2 wherein R is methyl.

4. The compound of any of Claims 1-3 wherein $R^1$ is $NH-R^2-R^3$.

5. The compound of any of Claims 1-4 wherein $R^2$ is C=O.

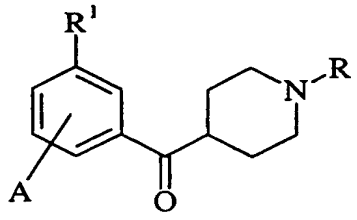
6. The compound of any of Claims 1-5 wherein $R^3$ is $Ar^3$.

7. The compound of any of Claims 1-6 wherein $Ar^3$ is 4-fluorophenyl.

8. The compound of any of Claims 1-6 wherein $Ar^3$ is 4-fluorophenyl additionally mono- or disubstituted.

9. The compound of any of Claims 1-6 wherein $Ar^3$ is selected from the group consisting of 2-iodo-4-fluorophenyl, 2-bromo-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2,4-difluorophenyl, and 2-methyl-4-fluorophenyl.

10. A pharmaceutical formulation comprising a compound of formula I:




I;

where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1-C_4$ alkyl, $C_3-C_6$ alkenyl, $C_3-C_6$ alkynyl, or (C1-C6 alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

$R^2$ is -CO-, -CS-, or $-SO_2-$;

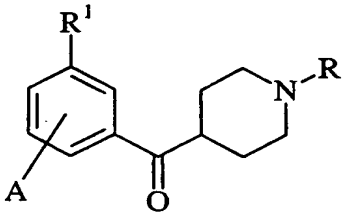
$R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring;

or a pharmaceutical acid addition salt thereof, and a pharmaceutical carrier, diluent, or excipient.

11. A method for activating $5\text{-}HT_{1F}$ receptors in mammals comprising administering to a mammal in need of such activation an effective amount of a compound of formula I:



I;

or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl, or (C1-C6 alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

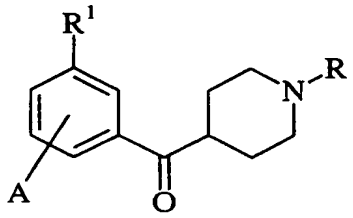
$R^2$ is -CO-, -CS-, or $-SO_2-$;

$R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring.

12. A method for inhibiting neuronal protein extravasation comprising administering to a mammal in need of such inhibition an effective amount of a compound of formula I:



I;

or a pharmaceutical acid addition salt thereof, where;

A is hydrogen, halo, $-OR^4$, $NH_2$, or $-CF_3$;

R is hydrogen, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl, or (C1-C6 alkyl)-$Ar^1$;

$R^1$ is $-NH-R^2-R^3$, hydroxy, $-OSO_2Ar^2$, or $NH_2$;

Ar, $Ar^1$, $Ar^2$, $Ar^3$, and $Ar^4$ are an optionally substituted phenyl or optionally substituted heteroaryl;

$R^2$ is -CO-, -CS-, or $-SO_2-$;

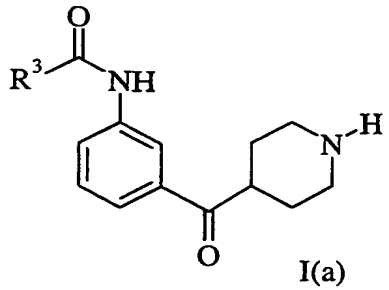
$R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$; provided $R^3$ is not hydrogen if $R^2$ is either -CS- or $-SO_2-$;

$R^4$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, or Ar; and

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring.

13. The method according to either of Claims 11 or Claim 12 where the mammal is a human.

14. A process of making the compounds of formula I(a):



I(a)

wherein $R^3$ is hydrogen, optionally substituted $C_1$-$C_6$ alkyl, $Ar^3$, $-NR^5R^6$, or $OR^5$;

$R^5$ and $R^6$ are independently hydrogen, optionally substituted $C_1$-$C_8$ alkyl, or $Ar^4$; or $R^6$ and $R^5$ combine, together with the nitrogen atom to which they are attached, to form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring; and

$Ar^3$ and $Ar^4$ are independently an optionally substituted phenyl or optionally substituted heteroaryl, comprising:

(a) protecting 4-benzoylpiperidine hydrochloride to form an N-protected 4-benzoylpiperidine hydrochloride;

(b) nitrating the N-protected 4-benzoylpiperidine hydrochloride to form a mixture of N-protected 4-(mono-nitrobenzoyl)piperidines;

(c) deprotecting the N-protected 4-(mononitrobenzoyl)-piperidine mixture to form a mixture of 4-(mononitrobenz-oyl)piperidines;

(d) separating the 4-(3-nitrobenzoyl)piperidine from the mixture of 4-(mononitrobenz-oyl)piperidines;

(e) reducing the 4-(3-nitrobenzoyl)piperidine to form 4-(3-aminobenzoyl)piperidine; and

(f) acylating the 4-(3-aminobenzoyl)piperidine.

15. The process of Claim 14 wherein steps a) and b) are combined.

16. The process of any of Claims 14-15 wherein the source of the protecting group of step a) is trifluoroacetic anhydride.

17. The process of any of Claims 14-16 wherein the source of the nitronium ion is ammonium nitrate.